

Molecular study in breast Paget's disease and its relationship with the prognosis: A retrospective-analytical study

Estudio molecular en la enfermedad de Paget de la mama y su relación con el pronóstico: Un estudio retrospectivo-analítico

Shokouh Taghipour Zahir¹ , **Mina Hesami²** , **Ali Gharaeikhezri³** , **Khatere Ghasemi⁴** , **Koorosh Rahmani³** , **Mohammad Hesam Gharaeikhezri³** , **Zahra Sahraneshin Samani³** 

1. Full Professor of Clinical and Surgical Pathology, Shahid Sadoughi university of medical sciences, Yazd, Iran

2. Prehospital and Hospital Emergency Research Center, Tehran University of Medical Sciences, Tehran, Iran

3. General Practitioner, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

4. Resident of pathology, Shahid Sadoughi university of Medical sciences, Yazd, Iran

Corresponding author

Khatere Ghasemi

E-mail: ghasemi_khatere@yahoo.com

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Abstract

Introduction: Paget's disease of the breast is a rare disease with an incidence of 0.5 to 5%. The role of molecular markers is not well understood in this type of cancer. Therefore, we decided to study the relationship between the status of molecular markers and the patient's prognosis and survival rates.

Materials and methods: This cross-sectional survival study was done by census sampling method. After collection, the data were entered into SPSS software version 18, and survival was assessed using Kaplan-Meier curves and Log-Rank test. P-value less than 0.05 was considered statistically significant.

Results: A total of 52 patients with a mean age of 48.89 ± 12.51 was obtained. 57.7% of patients had right breast involvement. 44 patients (84.6%) had infiltrating ductal carcinoma (IDC) and 3 patients (5.8%) had ductal carcinoma in-situ (DCIS). Thirty-five patient (67.3%) had a positive estrogen receptor, 29 patient (55.8%) had positive progesterone receptor and 32 patients (61.5%) were HER2neu positive. 14 patients (26.9%) have died. The mean survival time was 98.08 months and the one, two, three, four, and five-years survival rate were 92%, 85%, 80%, 73%, and 69%, respectively. There was a statistically significant difference between the mean survival rate and HER2neu status. So that the mean survival in HER2neu positive patients was significantly higher than HER2neu negative patients ($p < 0.002$).

Conclusion: Based on the findings of the study, it can be concluded that patients with Paget's disease have a long-life expectancy and HER2neu status is an effective factor in survival.

Key words: Breast cancer, Paget's disease, hormone receptors.

Resumen

Introducción: La enfermedad de Paget de la mama es una enfermedad rara con una incidencia del 0,5 al 5%. El papel de los marcadores moleculares no se conoce bien en este tipo de cáncer. Por ello, decidimos estudiar la relación entre el estado de los marcadores moleculares y el pronóstico y la supervivencia de las pacientes.

Materiales y métodos: Este estudio transversal de supervivencia se realizó mediante el método de muestreo censal. Tras la recogida, los datos se introdujeron en el programa informático SPSS versión 18, y la supervivencia se evaluó mediante curvas de Kaplan-Meier y la prueba de Log-Rank. El valor p menor de 0,05 se consideró estadísticamente significativo.

Resultados: Se obtuvo un total de 52 pacientes con una edad media de $48,89 \pm 12,51$ años. El 57,7% de las pacientes tenían afectación de la mama derecha. 44 pacientes (84,6%) tenían carcinoma ductal infiltrante (CDI) y 3 pacientes (5,8%) tenían carcinoma ductal in situ (CDIS). Treinta y cinco pacientes (67,3%) tenían un receptor de estrógeno positivo, 29 pacientes (55,8%) tenían un receptor de progesterona positivo y 32 pacientes (61,5%) eran HER2neu positivos. 14 pacientes (26,9%) fallecieron. El tiempo medio de supervivencia fue de 98,08 meses y la tasa de supervivencia a uno, dos, tres, cuatro y cinco años fue del 92%, 85%, 80%, 73% y 69%, respectivamente. Hubo una diferencia estadísticamente significativa entre la tasa de supervivencia media y el estado de HER2neu. Así, la supervivencia media de las pacientes HER2neu positivas fue significativamente mayor que la de las pacientes HER2neu negativas ($p < 0,002$).

Conclusiones: En base a los resultados del estudio, se puede concluir que los pacientes con enfermedad de Paget tienen una larga esperanza de vida y el estado de HER2neu es un factor efectivo de supervivencia.

Palabras clave: Cáncer de mama, enfermedad de Paget, receptores hormonales.

Introduction

Paget's disease of the breast is a type of breast neoplasm that affects the skin of the nipple. This disease, or rather breast cancer, in many cases was associated with a non-invasive ductal carcinoma of the mammary gland tissue, although it can also be associated with invasive cancer¹⁻⁵. The results of a study conducted in Turkey on patients with Paget's breast showed that in 63% of patients there is a palpable mass on examination, in 33% eczema, erythema, and nipple ulcer, and in 10% there is discharge from the breast⁶. Histologically, a multifocal or multicentric tumor was observed in 21% of patients⁷⁻⁹. The results of another study conducted in Thailand on 27 patients with Paget's disease showed that 11 patients with clinical symptoms of Paget's disease, of which 7 had palpable breast mass¹⁰. Results of Arafah M et al, showed that most of the patients with breast Paget's disease were positive for HER2neu receptor¹¹. Other studies conducted on Paget's disease showed that ER, PR, receptor expression in Paget's disease were lower than other types of breast carcinoma and survival of patients with Paget's disease alone was better than patients with underlying of invasive carcinoma¹²⁻¹⁴. Because Paget's disease of the breast is one of the diseases in which the role of molecular markers is not well understood; Our study aimed to investigate the molecular status of Paget's disease and its relationship with the patient's survival time and prognosis.

Materials and Method

This descriptive cross-sectional survival study was done on patients with Paget's disease of the breast during the years 2006 to 2018. After the approval of the dissertation in the ethics committee of the university (IR.SSU.MEDICINE.REC.1399.172) with a pre-prepared checklist that includes the variables under study such as age, side involvement, type of accompanying pathology, molecular status including; estrogen receptor, progesterone receptor, and HER2neu status, overall survival rate (the patient's life condition from the time of diagnosis until the end of the study). The necessary variables were extracted from patients' hospital folders and pathology reports and then the collected data were entered into the preparation checklist. Sampling was by census method and all patients with Paget's breast disease referred to the hospitals in Yazd were included in the study during the mentioned period. Patients whose files were incomplete and could not be accessed were excluded from the study. In case of incomplete files, the necessary information was requested by telephone.

Statistical Analysis:

All registered data were analyzed using SPSS software version 18 for Windows (SPSS, Chicago, IL) and analyzed using appropriate descriptive indicators (frequency

distribution, mean and median), ANOVA and Chi-square statistical tests. The survival rate was assessed by using Kaplan-Meier curves and Log-rank test. P value less than 0.05 was considered statistically significant.

Ethical Considerations:

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran and registered with the protocol number "IR.SSU.MEDICINE.REC.1399.172". Participants were provided written informed consent and were included in the study after they were provided information on treatment methods.

Results

In this study, 52 patients with a mean age of 48.89 ±12.51 years with a minimum age of 26 and maximum age of 78 years were obtained. Fourteen patients (26.9%) were in the age group under 40 years, 27 (51.9%) in the age group of 40 to 59 years, 11 (21.2%) in the age group equal or older than 60 years old. The frequency distribution of the involvement side in the studied patients showed that in 30 patients (57.7%) the tumor was on the right side and in 22 patients (42.3%) it was on the left side. The results of the study on the prevalence of comorbid cancer showed that 44 patients (84.6%) had infiltrated ductal carcinoma (IDC) and 3 patients (5.8%) had DCIS.

The results of the study on the frequency distribution of the type of receptor in the studied patients showed that 35 patients (67.3%) had estrogen receptors, 29 patients (55.8%) had progesterone receptors and 32 patients (61.5%) had HER2neu positive status. The results of the study on the frequency distribution of patient's mortality rate showed that at the end of the study, 38 patients (73.1%) were alive and 14 patients (26.9%) have died. The mean survival time of patients using the Kaplan-Meier curve with a 95% confidence interval (CI = 95%) was 98.08 months (8.06 years) with a minimum duration of 21 days and a maximum duration of 145 months (**Figure 1**). According to the **figure 1**, it can be seen that the survival of patients was equal to 118.87 months (or 9.77 years). Also, the survival rates of one, two, three, four, and five-years were 92%, 85%, 80%, 73%, and 69%, respectively. The results of the study on the mean survival time of patients in terms of age showed that the lowest survival rate was in the age group over 60 years (52.91 months). (**Figure 2**) Other information is given in **table I**. By using the Log Rank test, there is no statistically significant difference between the mean survival of patients according to age ($P>0.05$). The mean survival time of the patients in terms of side involvement showed that the mean survival in patients with right and left involved sides was 97.92 and 58.42 months, respectively. Other information is given in **table I**.

Figure 1: Mean survival time in the studied patients.

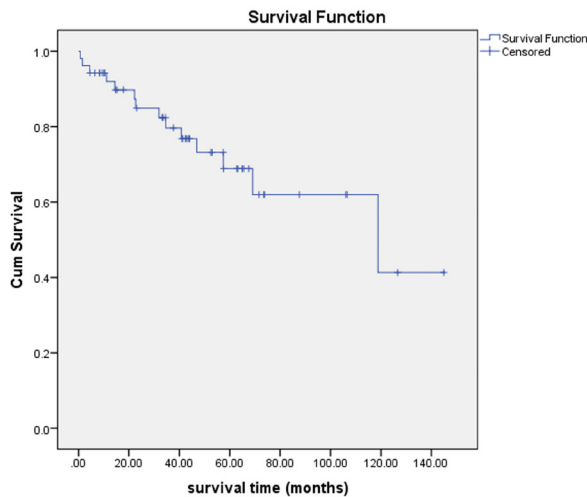


Figure 2: Mean survival time based on patient's age.

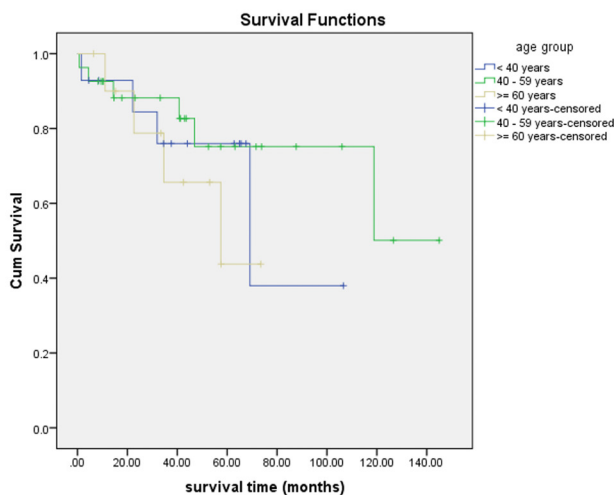


Figure 3: survival time based on Her2 neu status.

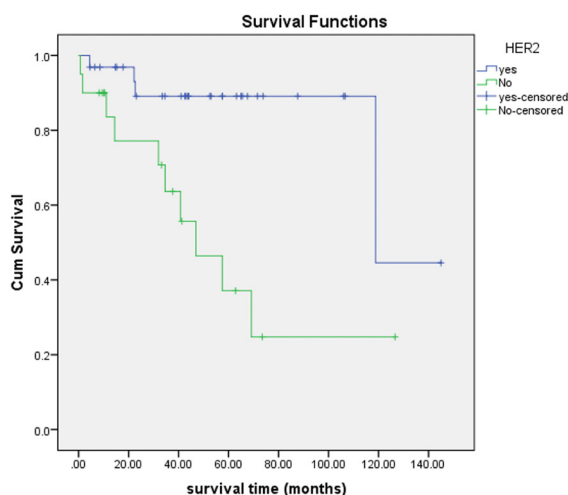


Table I: Molecular status in studied patients and correlation with survival time.

	number	Died (N)	Mean survival time (month)	P value
Estrogen receptor				
Positive	35	12	79.53	0.065
Negative	17	2	129.64	
Total	52	14	98.07	
Progesterone receptor				
Positive	29	8	87.39	0.715
Negative	23	6	108.74	
Total	52	14	98.07	
Her 2neu status				
Positive	32	4	119.44	0.002
Negative	20	16	59.78	
Total	52	20	98.07	

The mean survival time of the patients in terms of the estrogen receptor status, was 79.53 months for positive group and 129.65 months, for negative groups, respectively. Other information is given in **table I**. By using the Log Rank test, it showed that there was no statistically significant difference between the mean survival of patients in terms of estrogen receptor status ($P>0.05$). The results of the study on the mean survival time of patients in terms of progesterone receptor status showed that the mean survival in the group that had positive and negative progesterone receptors were 87.39 and 108.74 months, respectively. Other information is given in **table I**. There was no statistically significant difference between the mean survival rate of patients according to the status of progesterone receptor ($P>0.05$) (Log-rank test).

There was a statistically significant difference between the mean survival rate of patients according to HER2neu status ($P<0.05$); The mean survival in HER2neu positive patients (119.45) was significantly higher than HER2neu negative patients. **Figure 3**

Discussion

Paget's disease of the breast is a rare disease that first described by James Paget in 1874¹⁴. The most clinical manifestation of Paget's disease is a skin lesion in the nipple area. In most cases, this disease is associated with an in situ ductal carcinoma²⁻⁹. Different results have been reported in terms of progesterone and estrogen receptors¹⁵. HER2neu status can also affect patients' prognosis. The results of our study showed that the mean age of the patients was 48.89 ± 12.51 years and 51.9% of the patients were in the age group of 40 to 59 years. In the study conducted by Wang, the mean age of the patients was 51.8 years¹³. The results of another study conducted in Thailand showed that the mean age of patients was 50.31 and the age range of patients was 36-68 years¹². The results of both studies were in line with the results of our study. Paget's disease of the breast seems to occur more in the fifth and sixth decades of life. Previous studies

have reported a prevalence of cancer associated with Paget's disease from 67 to 100 percent; In most studies, more than 90% are reported. A study by Muttarrak on 27 patients with Paget's breast found that the prevalence of Paget's disease was 1.14% among patients with breast carcinoma¹². The results of our study on the prevalence of comorbid cancer showed that 44 patients (84.6%) had IDC and 3 patients (5.8%) had DCIS. The results of Wang's study showed that out of 137 patients, 7 had Paget's disease without any underlying cancer and 130 others had underlying cancer or DCIS¹³. The results of a study conducted in the Greece showed that 68.5% of patients with Paget's disease of the breast were simultaneous with DCIS or IDC¹⁴. As reported in previous studies, a high percentage of cases of Paget's disease is associated with underlying malignancy, and the most common malignancy associated with this disease was ductal carcinoma of the breast¹⁵⁻¹⁸. The results of the present study on the frequency distribution of receptor type in the studied patients showed that 35 patients (67.3%) had estrogen receptors, 29 patients (55.8%) had progesterone receptors and 32 patients (61.5%) were positive for HER2neu. The results of a study conducted in China showed that the positive rates of ER, PR, and HER2 neu were 29.2%, 38%, and 78.1%, respectively¹⁹. HER2neu seems to be the most common marker used in patients with Paget's disease of the breast. In a study conducted by Salvadori B et al. in 1976 on 91 patients with Paget's disease, it was found that the outcome of surgical treatment on the 5 and 10-year survival rates was 59% and 44%, respectively, as well as the average survival. Also, the average survival of patients was 9 years²⁰. The 5 and 10-year survival rates were 38% and 22% in patients with a palpable breast mass and 92% and 82% in patients without palpable mass, respectively²¹. Regarding the survival rate and prognosis of patients and the role of hormone receptors and other factors affecting the prognosis of the disease, the results of our study showed that 14 (26.9%) of patients died. The mean survival time in the studied patients was 98.08 months and the survival rates of one, two, three, four, and five-years were 92%, 85%, 80%, 73%, and 69%, respectively. There was a statistically significant difference between the mean survival of patients according to HER2neu status. The mean survival in HER2neu positive patients (119.45) was significantly higher than in HER2neu negative patients. In a study conducted by Ling H et al. in 2013 in China on 52 patients with Paget's breast and invasive breast carcinoma, it was found that 24 patients (46.2%) did not have clinical symptoms of Paget and the results showed that the presence of underlying carcinoma increased the risk of lymph node involvement, decreased expression of hormone receptors, increased expression of HER2neu and reduced the 5-year survival rate of patients⁹. The results of Wang study showed that the 2-year and 5-year survival rates were 99% and 96%, respectively¹³. There was a statistical relationship between the duration of the disease, HER2neu positivity, tumor stage and lymph node involvement, and metastasis with survival, which is

consistent with the present study. The results of another study showed that 92.9% of Paget cells were positive for the marker C-erbB-2, 100% for Cyclin D1, 85.7% for Ki-67, and 14.3% for Bcl-2. The results of this study also showed that the positive molecular markers of HER2neu, Cyclin D1, and Ki-67 in patients with Paget's disease were associated with greater invasiveness, worse prognosis, and lower survival rate¹⁹. Five- and ten-years survival rates in patients with palpable breast mass were 38% and 22%, respectively, and in patients without palpable mass were 92% and 82%, respectively. The results of the Ling H study showed that the presence of underlying carcinoma increased the risk of lymph node involvement, decreased expression of hormone receptors, increased expression of HER2neu, and decreased 5-year survival⁹.

Conclusion

According to the results of the study and the high average survival and 5-year survival rate of patients, it can be concluded that in general, Paget's disease of the breast has a good prognosis and the survival rate is high in these patients. Also, according to the results, it can be said that none of the variables of age, breast side involved, the status of hormone receptors (estrogen and progesterone) effects on the survival rate of patients with Paget disease, and the only effective factor on the survival rate is HER2neu status, so patients who are HER2neu positive have higher survival time.

Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this paper.

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Authors' contribution

Supervision and Project administration: Shokouh Taghipour Zahir

Conceptualization and Data curation

Khatere Ghasemi

Formal analysis and Writing - original draft and Writing - review & editing

Mohammad Shafiee, MINA HESAMI, ALI GHARAEIKHEZRI

Investigation and Methodology

Koorosh Rahmani

Visualization and Resources: Farzan Safi Dahaj, MOHMMADHESAM GHARAEIKHEZRI

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